II. REMARKS

Claims 1-65, 234-331 and 466-509 are all the claims pending in the application.

Claims 5, 8, 30, 54, 63, 278, 300, 320, 329, 241,255,269,276-278,296, 298-300,473,487,501 have been objected to because of various informalities.

Claims 1-65, 234-331 and 466-509 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite.

Rejection of claims 1, 18, 23-26, 41,46-49, 274,296,506 and 508 based on Barry under 35 USC § 102 (a) have been maintained .

Rejection of claims 1-3, 6-19, 22- 28, 41-42, 45-52, 55-61, 64-65, 234-2 35,246-249, 260-263, 2 74-2 76,279-292,295-298,301-312, 315-318, 321-327,330-61,466-467,478-481, 492-495 and 506-509 under 35 U.S.C. § 103 based on Barry in view of Fink have been maintained.

Rejection of claims 1-65, 234-3 31 and 466-55 under 35 U.S.C. § 103 (a) based on Barry in view of Fink and further in view of Thalhammer-Reyero has been maintained.

The objection to the oath has been maintained.

The Applicants traverse the rejections and request reconsideration of the amended claims.

The Applicants thank the Examiner for the personal interview dated January 14, 2002, and the suggestions made therein. The Applicants respectfully incorporate the suggestions made.

A. Formal Matters

The Applicants amend the claims to overcome the objections made by the Examiner. Regarding the objection to the oath, the Applicants' representatives raised the issue during the personal interview of January 14, 2002. The Examiner indicated during the interview that the

issue is still under consideration and that she would notify the Applicants soon whether the objection will be withdrawn in view of the Applicants position on the issue.

B. Section 112 Rejections

The Applicants respectfully amend the claims to overcome the section 112 rejections.

C. Prior Art Rejections

1. Section 102 Rejections over Barry

Rejection of claims 1, 18, 23-26, 41,46-49, 274,296,506 and 508 based on Barry under 35 USC § 102 (a) have been maintained .

Independent computer system claims 1 and 26 require a treatment protocol generator that is adapted to generate a plurality of treatment protocols. Likewise, independent computer-implemented method claims 274 and 296 require a step of enumerating a plurality of treatment protocols. Likewise independent computer program product claim requires a treatment protocol generator code to generate a plurality of treatment protocols.

Claims 28, 23-25, 41, 46-49 and 508 depend on the above independent claims and are patentable at least for the same reasons.

The Applicants amend the claims to clarify that in the present invention treatment protocols are generated. On the other hand, as agreed by the Examiner in the interview of January 14, 2002, Barry merely teaches selecting a treatment from "canned" treatment protocols.

Some significant differences between the present invention as recited in the above claims and Barry are discussed herein. Unlike the present invention, Barry teaches an "expert system" designated for guiding the selection of therapeutic treatment regimens. It does not calculate or

find the best (optimal) treatment but it helps the expert to choose one regimen out of many regimens stored in memory, which will be most appropriate ("optimal"). Barry is at best a database and a guiding system, rather than a tool of finding the optimal protocol. Barry asserts: "...An object of the invention is to provide systems, methods and computer program products for selecting therapeutic treatment regimens for patients in which available treatments are listed,...".

Barry teaches a database of known protocols for some known diseases. The protocols are fixed and are not calculated by means of the patent. It means that the protocols that are in the patent database are sort of prescription protocols; they are defined and determined. The system can consider any protocol, as long as it is pre-defined. In contrast, the present invention generates different possible protocols out of the almost infinite space of feasible protocols. In Barry, the merit of each protocol in this patent is not calculated, but determined in advance, by a group of expert. This pre-determined value may change only with respect to the medical history of the patient, more specifically with respect to previous treatments. In contrast, in the present invention the value of each protocol by evaluating the simulated evolution of the disease this protocol creates.

Also, in Barry, each of the proposed protocols may include some warnings or comments (advisories). These comments are pre-associated with the previously known effects of the protocols. In contrast, in the present invention, since each protocol is evaluated through the simulation it creates, any expert could easily infer and learn of any potential problem a given protocol may inflict.

In Barry, the selected protocol in this patent is one of a set of pre-determined protocols. In our model, the selected protocol is completely unknown in advance (it is calculated).

Barry uses rules in order to evaluate (rank) protocols and / or disqualify protocols. These rules are authored by a clinical advisory panel of physicians and scientists and they are:

a. Objective rules: based on industry-established facts regarding the treatment and are drawn from the package insert information of the drug manufacturers and from peer reviewed and published journal articles.

b. Subjective rules: based on expert opinions, observations and experience.

c. Data-base generated rules: derived from the outcomes of patients tracked in the system who received known and defined therapies and either improved, stabilized or worsened during a defined period.

The present invention does not use any strict rule in order to evaluate a protocol. Rather, the goal function concretely evaluates the performance of the simulated dynamics under each simulated protocol. The goal function is one formula in which different criteria, are mathematically formulated and subtly weighted.

Barry does not simulate any biological processes. Rather, the data composing the medical history of the patient are entered manually. In the present invention, they are calculated through a model and by a simulation. One advantage of the present invention, unlike in Barry, is that the present invention can evaluate different, novel routes of delivery.

Barry is used as an artificial intelligence system that can simulate the judgment and behavior of a human or an organization that has expert knowledge and experience in a particular field. However, such an approach can not accomplish a major feature of the present invention that is helping in finding new protocols (or aspects of treatments), which were not considered

before. Another advantage is that the present invention can help in evaluating hypothetical drugs, while Barry can only deal with drugs that are used in its "canned" database of treatments.

The points raised by the Examiner in the pending Office Action are discussed herein 1. In Page 14, Parag. 2, line 4 – the Examienr asserts …"Barry teaches…a knowledge-base of expert rules…". However, Barry uses knowledge-base of expert rule, publically known. The rules governing the mathematical terms of the present invention are not predetermined rules .

In Page 14, Parag. 2, line 4 – the Examiner notes that Barry uses a knowledgebase…"for determining available treatment options". In contrast, the present invention does not select the optimal treatment out of a repertoire of AVAILABLE treatments but, rather, generate a protocol space including mostly new treatments that have not been tried before. Barry does not provide a method to simulate new treatments.

Unlike what the Examiner asserts about Barry in Page 14, Parag. 2, line 5 as being an expert system, the present invention is not an expert system; it adds new insights rather than replacing human decision-making.

While the Examiner notes in Page 14, Parag. 2, line 6 that Barry …"can simulate the judgement and behaviour of human…", the output of the present system can never be predicted by human intuition. The present system simulates disease processes and physiological processes and these can occur in human as well as in dogs, pigs, monkeys or mice, etc. This is by no means the simulation of human judgment as in Barry.

While, as noted by the Examiner in Page 14, Parag. 2, line 7…"the expert system contains a knowledge-base and a set of rules", the present invention contains 1. a set of mathematical formulae 2. a set of input biological and pharmacological parameters; 3. an

optimization tool. They all cooperate to provide a simulation of a biological system rather than an expert system. Unlike an expert system, which simulates human behavior, the present system is based on simulating diseases and physiological dynamics.

D. Section 103 Rejections

1. Rejection over Barry and Fink

Claims 1-3, 6-19, 22- 28, 41-42, 45-52, 55-61, 64-65, 234-2 35,246-249, 260-263, 2 74-2 76,279-292,295-298,301-312, 315-318, 321-327,330-61,466-467,478-481, 492-495 and 506-509 have been rejected under 35 U.S.C. § 103 based on Barry in view of Fink.

The above claims are either dependent on the claims listed as being rejected under section 102 and/or include the limitation related to "generation of treatment protocols". As admitted by the Examiner Barry does not teach such a generation. The Applicants respectfully submit that Fink does not overcome this deficiency. Therefore, the arguments raised in relation to the section 102 rejection are equally valid.

Further, Fink asserts, "object of the present invention to provide a system and method for modeling biological systems and disease processes....for modeling biological system in a manner reflecting...for representing a biological system in a hierarchical manner..."(column 2, line 55-65) – Fink provides a system for modeling and is focused on the advantages that can be achieved when combining several modules in a way that represents a biological system.

In the present Specification, by "model of a biological process", what is meant is a chain of expressed procedures, which are formulated in such a way, that it can be analyzed as representing a well defined biological process. The patent of Fink is not a model, since there are no specific expressed procedures.. Fink patent could be summarized by the following citation: "It

is therefore an object of the present invention to provide a system and method for modeling biological systems and disease processes."

In Page 15, Parag. 3, line 3, the Examiner asserts –…"Fink… Integrates all of the biological relationships…". In the present invention integrating all of the biological relationships is not contemplated. In contrast, very specific relationships are integrated. This difference is the significant difference between a representation system as taught by Fink and specific models as in the present invention. The Applicants respectfully submit that finding the present invention unpatentable because of representation systems like Fink (or Thalhammer) is like denying authorship to a writer because all the words he used previously appeared in the English dictionary.

In Page 15, Parag. 3, line 7 and in several other instances the Examiner incorrectly asserts that…"Fink also teaches that her model". To the contrary, Fink does not provide a model, but, rather, a system and method for modeling… (see col 2, line 55-65).

It is believed that the Examienr's characterization in Page 15, Parag.3 line 9 – …"A dynamic model which integrates all the known biological relationships with regard to a particular disease " is overbroad. This would lead to the incorrect conclusion that Fink suggests a model of an infinite number of reactions. Such a model is impractical to say the least. Therefore, the Examiner is respectfully requested to reconsider her characterization of Fink.

While Fink may at best provide a system for accommodating models, no specific model is suggested.

In Page 17, Parag. 1, line 9, the Examiner asserts that…"both Barry and Fink teach use of their model to predict optimal treatment…" Oxford dictionary defines optimum as best, or most

favorable . On the other hand, Barry, at best, compares between documented treatments. As can be clearly determined, known treatments constitute only a negligible portion of all potential treatments. Fink does not provide any method of selecting treatments at all. Moreover, Barry + Fink does not have any added value.

If Fink suggested recommending the optimal treatment then Barry would have been redundant. Otherwise, if Fink does not provide the optimal treatment then Barry using Fink's results cannot yield the optimal treatment because the output given by Fink is not the optimal solution. Using Barry's patent one acknowledges the need to treat a specific patient with a specific treatment. To this Fink's representation tool can ad very little. If, indeed, Barry could provide an optimal treatment, then that would have sufficed and any further simulation and treatment suggestion would have been sub-optimal by definition. Therefore, the Examiner's argument is believed to be self-contradictory. The present invention provides for the optimum out of a very large number of potential treatments, so that every potential treatment is considered.

On page 17, Parag. 1, line 14-16, the Examiner incorrectly asserts that ..." As Fink's model is one which evaluates therapeutic treatments". The Applicants respectfully submit that Fink does not teach any such evaluation method.

Again the Examiner is mischaracterizing Fink by asserting on Page 17, Parag. 1, line 1 that " In response...Fink teaches that her model can be used to demonstrate the course of a particular disease..." As mentioned above, Fink is a tool, it is not a model which makes specific claims. ONE general model for representing any disease can not be created since a disease model makes a set of particular claims about the process of a given disease and a general disease model

necessarily theorize that all diseases are the same. Particular disease claims do not appear in Fink. Hence Fink is NOT a disease model.

2. Section 103 rejection over Barry, Fink and Thalhammer-Reyero.

All the pending claims have been rejected over Barry/Fink in view of Thalhammer-Reyero.

The Applicants respectfully submit that Thalhammer-Reyero does not cure the above-noted deficiencies in the teachings of Barry/Fink.

In Page 18, Parag. 3, line 7-9, the Examiner asserts that..." Thalhammer-Reyoro ...is relied upon for her teaching of modeling cells in an integrated computer-based system". Thalhammer-Reyoro et al. (hereinafter T-R) , provides a representation tool for describing intra-cellular biochemical processes. The present invention accounts for sub-cellular level only as far as monitoring the transition of cells through by the cell division cycle. Therefore, the Applicants respectfully submit that, there is no overlap whatsoever, between the teaching of T-R and ours.

The Applicants respectfully submit that the Examiner's assertion on Page 18, Parag. 3, line 10, "and her teaching that modeling cell-state and transition is of major importance in simulating the behavior of biological systems" is over broad. It is unclear as to what extent the Examiner is generalizing the above alleged teaching. In the present invention the behavior of specified biological systems (eg., bone-marrow blood formation) is simulated without having the need to describe any of the processes refered to by T-R.

On Page 18, Parag. 3, line 11-16 the Examiner asserts " In response...G1 state cells can be further compartmentalized...". The Applicants respectfully submit that (sub)compartmentalization is a common procedure in any sorting behavior. However, an entity

can be (sub)compartmentalized in many different ways. Clearly, the ways of (sub)compartmentalization used in the present invention are different from those of T-R, who, in the cited reference (col. 23, l.35-40), writes: 'G1.1-compartment represents activated cells or early-G1-Phase-cells which have recently entered G1-phase of cell-cycle, as characterized by transcription of early response genes, expression of new receptors;' etc. Clearly, T-R's patent is focused on the capacity to model intra-cellular biochemical pathways, possibly involving gene expression. In contrast, in the present invention there is no reference to any biochemical pathway.

On Page 19, Parag. 1, line 6 - et seq, the Examiner asserts..." information taught by each reference may have successfully been combined as all teach computer systems and methods for predicting various biological functions". In contrast, Barry teaches simulation of human decision-making, which is based on the knowledge of patients parameters taken at certain time-points, in conjunction with knowledge of known medical treatments and their known consequences. So, for example, suppose Barry's expert system suggests a given treatment which is adequate for a patient having, say a certain viral disease with a measured viral load, say x particles/ ml3. The Applicants respectfully submit that neither in Fink nor T-R this information can be input and further manipulated? This is at least because Fink and T-R do not provide any disease model even though the word model is often used by Fink, when it refers to a tool. Both Fink and T-R teach tools where various biological models can be implemented. However, this combination cannot be complemented by Barry because the actual implementation in a potential Fink-T-R combination, that is, the models themselves, is not provided by these authors, so that a "simulation pipeline" were to plug the expert system of Barry is still missing.

Further, the Examiner is completely silent about the specific limitations in claims 238-245, 247, 252-259, 261, 266-273,470-477, 479,484-491, 493,498-505. Specifically, each of claims 238, 252, 266, 470, 484 and 498 require that a stepwise equations be used. The rest of the claims in the above list depend from 238, 252, 266, 470, 484 and 498 and contain further specific limitations. The Examiner admits that Barry/Fink/Thalhammer-reyero does not teach stepwise equations. The Applicants respectfully submit that the combined references do not teach any of the further limitations of the claims in the above list.

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

Applicant hereby petitions for any extension of time which may be required to maintain the pendency of this case, and any required fee, except for the Issue Fee, for such extension is to be charged to Deposit Account No. 19-4880.

Respectfully submitted,

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APPENDIX

VERSION WITH MARKINGS TO SHOW CHANGES MADE

a) IN THE CLAIMS:

The claims are amended as follows:

1. (Amended) A computer system for recommending an optimal treatment protocol for an individual , said system interfacing with the computer and said system further comprising:

a system model;

a treatment protocol generator adapted to generate a plurality of treatment protocols;

a system model modifier, wherein said [system model is modified by the] system model modifier is adapted to modify said system model based on parameters specific to the individual; and

a selector adapted to select an optimal treatment protocol from said plurality of treatment protocols based on the modified system model.

2. (Amended) The system of claim 1 wherein the system model further comprises:

a [realistic] biological process model; and

a [realistic] treatment model that is adapted to model [models the] effects of a treatment on said biological process.

3. (Amended) The system of claim 2, wherein said biological process model comprises mathematical models for biological processes affecting healthy cell populations and biological processes affecting diseased cell populations with at least one disease.

5. (Twice amended) The system of claim 3 wherein said diseased cell populations [with at least one disease] is one of cancer cells, and diseased bone-marrow cells [including diseased Neutrophill cells and diseased Thrombocyte cells].

6. (Amended) The system of claim 2, wherein said treatment [models comprise] model comprises treatment specific processes that affect cell populations.

7. (Amended) The system of claim 6 wherein said treatment specific process [is] comprises interactions and associated biological processes involving one of a group [comprising] consisting of pharmacokinetic interactions and processes , pharmacodynamic interactions and processes , cytostatic interactions and processes, cytotoxic interactions and processes, and methods of affecting cell biology and causing cell death or cell replication [, with associated biological processes].

8. (Twice Amended) The system of claim 1 wherein, said parameters specific to the individual [include] includes one [or more] selected from a group consisting of parameters related to [the] biological process dynamics, patient specific drug pharmacokinetics [PK], pharmacodynamics [PD], and dynamics of dose-limiting host tissues.

10. (Amended) The system of claim 1, wherein the selector [incorporates] is adapted to incorporate user-specific parameters in performing selection.

11. (Amended) The system of claim 10 wherein said [incorporation is done] selector is adapted to incorporate user-specific parameters by using a fitness function.

12. (Amended) The system of claim 11 wherein said fitness function [incorporates] adapted to incorporate at least one parameter selected from a group [comprising] consisting of patient survival, time to death, time to reach a specified disease stage [(including cure)], tumor load, pathogen load, cytotoxicity, side effects, quality of life, cost of treatment, and pain.

13. (Amended) The system of claim 12, wherein [a user can input] the system is adapted to receive user input for specific coefficients for said at least one parameter and the system is further adapted to adjust the fitness function to satisfy the user's goals.

17. (Amended) The system of claim 1 wherein said system is adapted to consider cytotoxic effects during selection of treatment protocols [incorporate cytotoxic effects].

18. (Amended) The system of claim 1 wherein said system is adapted to consider drug efficacy during selection of treatment protocols [incorporate drug efficacy].

19. (Amended) The system of claim 1, wherein the selector [performs] is adapted to use operation research methods for the selection [using operation research methods].

20. (Amended) The system of claim 1, wherein the selector further comprises heuristics, said [heuristics being used to perform searching and selection] selector being adapted to use the heuristics for searching and selection.

22. (Amended) The system of claim 1 wherein said recommendation [is] comprises a combination of disease and treatment strategy, [including types of treatment, e.g. chemotherapy, radiotherapy, surgery, immunotherapy, etc, device, drug or drug combination and treatment schedule and dosage] wherein said treatment strategy includes at least one of types of treatment, device, drug combination, treatment schedule and dosage.

23. (Amended) The system of claim 1, wherein, said system is adapted to be implemented over a distributed computing system.

25. (Amended) The system of claim 23, wherein [a user uses the system remotely] the system is adapted to be used remotely by a user.

26. (Amended) A computer system for recommending an optimal treatment protocol for a general patient, said system interfacing with the computer and said system further comprising:

a system model;

a treatment protocol generator adapted to generate a plurality of treatment protocols; and

a selector to select an optimal treatment protocol from said plurality of treatment

protocols based on the system model.

27. (Amended) The system of claim 26 wherein the system model further comprises:

a [realistic] biological process model; and

a [realistic] treatment model that is adapted to model [models] the effects of a treatment on said biological process.

28. (Amended) The system of claim 27, wherein said biological process model comprises mathematical models for biological processes affecting healthy cell populations and biological processes affecting diseased cell populations with at least one disease.

30. (Amended) The system of claim 28 wherein said diseased cell populations [with at least one disease] is one of cancer cells, and diseased bone-marrow cells [including Neutrophill cells and diseased Thrompocyte cells].

31. (Amended) The system of claim 27, wherein said treatment [models comprise] model comprises treatment specific processes that affect cell populations.

32. (Amended) The system of claim 31 wherein said treatment specific process [is] comprises interactions and associated biological processes involving one of a group [comprising] consisting of pharmacokinetic interactions and processes , pharmacodynamic interactions and processes , cytostatic interactions and processes, cytotoxic interactions and processes, and

methods of affecting cell biology and causing cell death or cell replication [, with associated biological processes].

33. (Amended) The system of claim 26, wherein the selector [incorporates] is adapted to incorporate user-specific parameters in performing selection.

34. (Amended) The system of claim 33 wherein said [incorporation is done] selector is adapted to incorporate user-specific parameters by using a fitness function.

35. (Amended) The system of claim 34 wherein said fitness function [incorporates] is a function of at least one parameter selected from a group [comprising] consisting of patient survival, time to death, time to reach a specified disease stage [(including cure)], tumor load, pathogen load, cytotoxicity, side effects, quality of life, cost of treatment and pain.

36. (Amended) The system of claim 35, wherein [a user can input] the system is adapted to receive user input for specific coefficients for said at least one parameter and the system is further adapted to adjust the fitness function to satisfy the user's goals.

40. (Amended) The system of claim 26 wherein said system is adapted to consider cytotoxic effects during selection of treatment protocols [incorporate cytotoxic effects].

41. (Amended) The system of claim 26 wherein said system is adapted to consider drug efficacy during selection of treatment protocols [incorporate drug efficacy].

42. (Amended) The system of claim 26, wherein the selector is adapted to use operation research methods for [performs] the selection [using operation research methods].

43. (Amended) The system of claim 26, wherein the selector further comprises heuristics, said [heuristics being used to perform searching and selection] selector being adapted to use the heuristics for searching and selection.

45. (Amended) The system of claim 26 wherein said recommendation is a combination of disease and treatment strategy, [including types of treatment, e.g. chemotherapy, radiotherapy, surgery, immunotherapy, etc, device, drug or drug combination and treatment schedule and dosage] wherein said treatment strategy includes at least one of types of treatment, device, drug combination, treatment schedule and dosage.

46. (Amended) The system of claim 26, wherein, said system is adapted to be implemented over a distributed computing system.

48. (Amended) The system of claim 46, wherein [a user uses the system remotely] the system is adapted to be used remotely by a user.

50. (Amended) A computer system for predicting progression of a biological process in an individual patient under a plurality of treatment protocols, said computer system interfaces with a computer, wherein said biological process [could be] is related to healthy or diseased processes, one of said plurality of protocols [including] being no treatment, said computer system comprising:

a system model;

a protocol generator for generating a plurality of treatment protocols; and

a system model modifier, wherein said [system model is modified by the] system model modifier is adapted to modify said system model based on parameters specific to the individual.

a predictor to predict the progression of at least one of the disease and the natural biological process under said plurality of treatment protocols based on the modified system model.

51. (Amended) The system of claim 50 wherein the system model further comprises:

a [realistic] biological process model; and

a [realistic] treatment model that models the effects of a treatment on said biological process.

52. (Amended) The system of claim 51, wherein said biological process model comprises mathematical models for biological processes affecting healthy cell populations and biological processes affecting diseased cell populations [with at least one disease].

54. (Amended) The system of claim 52 wherein said diseased cell populations [with at least one disease] is one of cancer cells, and diseased bone-marrow cells [diseased at least one of Neutrophill cells and diseased Thrombocyte cells].

55. (Amended) The system of claim 51, wherein said treatment [models comprise] model comprises treatment specific processes that affect cell populations.

56. (Amended) The system of claim 55 wherein said treatment specific process is interactions and associated biological processes involving one of a group [comprising] consisting of pharmacokinetic interactions and processes , pharmacodynamic interactions and processes , cytostatic interactions and processes, cytotoxic interactions and processes, and methods of affecting cell biology and causing cell death [, with associated biological processes].

57. (Amended) The system of claim 50 wherein, said parameters specific to the individual include one or more selected from a group consisting of parameters related to [the] biological process dynamics, patient specific drug pharmacokinetics [PK], pharmacodynamics [PD], and dynamics of dose-limiting host tissues.

59. (Amended) A computer system for predicting progression of a biological process in a general patient under a plurality of treatment protocols, wherein said biological process [could be] is healthy or diseased processes, said plurality of protocols including no treatment, , said system interfacing with the computer and said system further ,said computer system

comprising:

a system model;

a treatment protocol generator adapted to generate a plurality of treatment protocols; and

a predictor to predict the progression of the disease or [the] a natural biological process under said plurality of treatment protocols.

60. The system of claim 59 wherein the system model further comprises:

a [realistic] biological process model; and

a [realistic] treatment model that models the effects of a treatment on said biological process.

61. (Amended) The system of claim 60, wherein said biological process model comprises mathematical models for biological processes affecting healthy cell populations and biological processes affecting diseased cell populations with at least one disease.

63. (Amended) The system of claim 62 wherein said diseased cell populations [with at least one disease] is one of cancer cells, and diseased bone-marrow cells [including diseased Neutrophilll cells and diseased Thrombocyte cells].

64. (Amended) The system of claim 60, wherein said treatment [models comprise] model comprises treatment specific processes that affect cell populations.

65. (Amended) The system of claim 64 wherein said treatment specific process is interactions and associated biological processes involving one of a group [comprising] consisting of pharmacokinetic interactions and processes , pharmacodynamic interactions and processes , cytostatic interactions and processes, cytotoxic interactions and processes, and methods of affecting cell biology and causing cell death or cell replication [, with associated biological processes].

234. (Amended) A computer system for recommending an optimal treatment protocol for treating cancer using drugs, [including chemotherapy,] for an individual, , said system interfacing with the computer and said system further comprising:

a cancer system model;

a treatment protocol generator for generating a plurality of treatment protocols for treating cancer using chemotherapy;

a system model modifier, wherein said [cancer system model is modified by] the system model modifier is adapted to modify said cancer system model based on parameters specific to the individual; and

a selector adapted to select an optimal treatment protocol from said plurality of treatment protocols based on the modified system model.

235. (Amended) The system of claim 234 wherein the system model further comprises:

a [realistic] process model of cancer development; and

a [realistic] treatment model that is adapted to model [models] the effects of treating

cancer with drugs, including chemotherapy.

237. (Amended) The system of claim 235 where a tumor cell cycle is divided into at least four compartments G1, S, G2 and M and a quiescent stage is denoted by G0, wherein each of said four compartments is further subdivided into sub-compartments and an i^{th} sub-compartment representing cells of age I in the corresponding compartment, wherein the system is adapted to ensure that cells entering a compartment always enter a first sub-compartment of the compartment.

238. (Amended) The system of claim 237 wherein the model is adapted to trace [traces] development of cancer cells using a predetermined set of parameters by calculating a number of cells in each subcompartment using stepwise equations.

239. (Amended) The system of claim 238 wherein the system is adapted to use a probability vector is used to determine a fraction of cells that leaves any subcompartment in a compartment to move to a first subcompartment of the next compartment.

240. (Amended) The system of claim 238 where the system includes a set control functions that are adapted to uniquely determine an outcome of every single step, wherein said control functions [depend on] comprise age of cells, state of a current population and associated environment.

248. (Amended) A computer system for predicting [the] a progression of cancer in individual patients, said system interfacing with the computer and said system further comprising:

a cancer system model;

a treatment protocol generator to generate a plurality of treatment protocols for treating cancer using drugs [, including chemotherapy];

a system model modifier, wherein [said cancer system model is modified by the] system model modifier is adapted to modify said system model based on parameters specific to the individual; and

a predictor to predict the progression of cancer under the plurality of treatment protocols based on the modified system model.

249. (Amended) The system of claim 248 wherein the system model further comprises:

a [realistic] process model of cancer development; and

a [realistic] treatment model that [models] is adapted to model the effects of treating cancer with drugs [, including chemotherapy].

251. (Amended) The system of claim 249 where a tumor cell cycle is divided into at least four compartments G1, S, G2 and M and a quiescent stage is denoted by G0, wherein each of said four compartments is further subdivided into sub-compartments and an i^{th} sub-compartment representing cells of age i in the corresponding compartment, wherein the system is adapted to ensure that cells entering a compartment always enter a first sub-compartment of the

compartment.

252. (Amended) The system of claim 251 wherein the model is adapted to trace [traces] development of cancer cells using a predetermined set of parameters by calculating a number of cells in each subcompartment using stepwise equations.

253. (Amended) The system of claim 252 wherein the system is adapted to use a probability vector is used to determine a fraction of cells that leaves any subcompartment in a compartment to move to a first subcompartment of the next compartment.

254. (Amended) The system of claim 252 where the system includes a set control functions that are adapted to uniquely determine an outcome of every single step, wherein said control functions [depend on] comprise age of cells, state of a current population and associated environment.

255. (Amended) The system of claim 252 wherein the system comprises a model representing a tumor [is modelled as] the model comprising a plurality of [homogeneous group] groups of cells, each of said [homogeneous group] groups of cells representing a similarly behaving group of cells distributed between all the cell-cycle compartments.

256. (Amended) The system of claim 255, wherein the system is adapted to calculate in each step, a number of cells in each sub-compartment of each compartment of each group [is

calculated] according to factors including a previous state, parameters of tumor, tumor current microenvironment and drug concentration.

258. (Amended) The system of claim 257, wherein the system is adapted to incorporate pharmacokinetic [PK] and pharmacodynamic [PD], cytotoxic effects and cytostatic effects of anticancer drugs [are incorporated into the model].

259. (Amended) The system of claim 258 wherein the system is adapted to incorporate a dose-limiting toxicity [is incorporated] into the model.

260. (Amended) The system of claim 248 wherein, said parameters specific to the individual comprise parameters related to tumor dynamics, patient specific drug pharmacokinetic [PK], pharmacodynamic, and dynamics of dose-limiting host tissues.

262. (Amended) A computer system for predicting the a progression of cancer in a general patients, said system interfacing with the computer and said system further comprising:

a cancer system model;

a treatment protocol generator to generate a plurality of treatment protocols for treating cancer using drugs[, including chemotherapy]; and

a predictor to predict the progression of cancer under the plurality of treatment protocols based on the modified system model.

263. (Amended) The system of claim 262 wherein the system model further comprises:

a [realistic] process model of cancer development; and

a [realistic] treatment model that is adapted to model [models] the effects of treating cancer with drugs, including chemotherapy.

265. (Amended) The system of claim 263 where a tumor cell cycle is divided into at least four compartments G1, S, G2 and M and a quiescent stage is denoted by G0, wherein each of said four compartments is further subdivided into sub-compartments and an ith sub-compartment representing cells of age I in the corresponding compartment, wherein the system is adapted to ensure that cells entering a compartment always enter a first sub-compartment of the compartment.

266. (Amended) The system of claim 265 wherein the model is adapted to trace [traces] development of cancer cells using a predetermined set of parameters by calculating a number of cells in each subcompartment using stepwise equations.

267. (Amended) The system of claim 266 wherein the system is adapted to use a probability vector is used to determine a fraction of cells that leaves any subcompartment in a compartment to move to a first subcompartment of the next compartment.

268. (Amended)The system of claim 266 where the system includes a set control functions that are adapted to uniquely determine an outcome of every single step, wherein said

control functions [depend on] comprise age of cells, state of a current population and associated environment.

269. (Amended) The system of claim 266 wherein the system comprises a model representing a tumor [is modelled as] the model comprising a plurality of [homogeneous group] groups of cells, each of said [homogeneous group] groups of cells representing a similarly behaving group of cells distributed between all the cell-cycle compartments.

270. (Amended) The system of claim 269, wherein the system is adapted to calculate in each step, a number of cells in each sub-compartment of each compartment of each group [is calculated] according to factors including a previous state, parameters of tumor, tumor current microenvironment and drug concentration.

272. (Amended) The system of claim 271, wherein the system is adapted to incorporate pharmacokinetic [PK] and pharmacodynamic [PD], cytotoxic effects and cytostatic effects of anticancer drugs [are incorporated into the model].

273. (Amended) The system of claim 272 wherein the system is adapted to incorporate a dose-limiting toxicity [is incorporated] into the model.

274. (Amended) A computer-implemented method of recommending an optimal treatment protocol for an individual comprising:

creating a system model;

enumerating a plurality of treatment protocols;

modifying the system model based on parameters specific to the individual; [and]

selecting an optimal treatment protocol from said plurality of treatment protocols based on the modified system model and

recommending said optimal treatment.

275. (Amended) The method of claim 274 wherein the step of creating the system model further comprises:

modelling a biological process; and

[realistically] modelling effects of a treatment on said biological process.

276. (Amended) The method of claim 275, wherein said modelling of biological processes is done by [mathematical] mathematically modelling biological processes affecting healthy cell [populationss] populations and mathematically modelling biological processes affecting diseased cell [populationss] populations with at least one disease.

277. (Amended) The method of claim 276 wherein said healthy cell [populationss] populations include bone-marrow cells and host tissue cells that are affected by said treatment model.

278. (Amended) The method of claim 276 wherein said diseased cell [populationss] populations [with at least one disease] is one of cancer cells, and diseased bone-marrow cells [including diseased Neutrophill cells and diseased Thrompocyte cells].

279. (Amended) The method of claim 275, wherein said treatment models comprise treatment specific processes that affect cell[populationss] populations.

280. (Amended) The method of claim 279 wherein said treatment specific process is interactions and associated biological processes involving one of a group [comprising] consisting of pharmacokinetic interactions and processes , pharmacodynamic interactions and processes , cytostatic interactions and processes, cytotoxic interactions and processes, and methods of affecting cell biology and causing cell death or cell replication [, with associated biological processes].

281. (Amended) The method of claim 274 wherein, said parameters specific to the individual include one or more selected from a group consisting of parameters related to [the] biological process dynamics, patient specific drug pharmacokinetics [PK], pharmacodynamics [PD] and dynamics of dose-limiting host tissues.

285. (Amended) The method of claim 284 wherein said fitness function incorporates at least one parameter selected from a group consisting patient survival, time to death, time to reach a specified disease stage [(including cure)], tumor load, pathogen load, cytotoxicity, side effects,

quality of life, cost of treatment and pain.

290. (Amended) The method of claim 274 wherein said system is adapted to consider cytotoxic effects during selection of treatment protocols [incorporate cytotoxic effects].

291. (Amended) The method of claim 274 wherein said system is adapted to consider drug efficacy during selection of treatment protocols [incorporate drug].

295. (Amended) The method of claim 274 wherein said recommendation is a combination of disease and treatment strategy, [including types of treatment, e.g. chemotherapy, radiotherapy, surgery, immunotherapy, etc, device, drug or drug combination and treatment schedule and dosage] wherein said treatment strategy includes at least one of types of treatment, device, drug combination, treatment schedule and dosage.

296. A [Method] computer-implemented method of recommending an optimal treatment protocol for a general patient comprising:

creating a system model;

enumerating a plurality of treatment protocols; [and]

selecting an optimal treatment protocol from said plurality of treatment protocols based on the modified system model; and

recommending said optimal treatment.

297. (Amended) The method of claim 296 wherein the step of creating the system model further comprises:

modelling a biological process; and

[realistically] modelling effects of a treatment on said biological process.

298. (Amended) The method of claim 297, wherein said modelling of biological processes is done by [mathematical] mathematically modelling biological processes affecting healthy cell [populationss] populations and mathematically modelling biological processes affecting diseased cell [populationss] populations with at least one disease.

299. (Amended) The method of claim 298 wherein said healthy cell [populationss] populations include bone-marrow cells and host tissue cells that are affected by said treatment model.

300. (Amended) The method of claim 298 wherein said diseased cell [populationss] populations with at least one disease is one of cancer cells, and diseased bone-marrow cells [including diseased Neutrophill cells and diseased Thrompocyte cells].

301. (Amended) The method of claim 297, wherein said treatment models comprise treatment specific processes that affect cell[populationss] populations.

302. (Amended) The method of claim 301 wherein said treatment specific process is interactions and associated biological processes involving one of a group [comprising] consisting of pharmacokinetic interactions and processes , pharmacodynamic interactions and processes , cytostatic interactions and processes, cytotoxic interactions and processes, and methods of affecting cell biology and causing cell death [, with associated biological processes].

305. (Amended) The method of claim 304 wherein said fitness function incorporates at least one parameter selected from a group [comprising] consisting of patient survival, time to death, time to reach a specified disease stage [(including cure)], tumor load, pathogen load, cytotoxicity, side effects, quality of life, cost of treatment and pain.

310. (Amended) The method of claim 296 wherein said system is adapted to consider cytotoxic effects during selection of treatment protocols [incorporate cytotoxic effects].

311. (Amended) The method of claim 296 wherein said system is adapted to consider drug efficacy during selection of treatment protocols [incorporate drug efficacy].

315. (Amended) The method of claim 296 wherein said recommendation is a combination of disease and treatment strategy, [including types of treatment, e.g. chemotherapy, radiotherapy, surgery, immunotherapy, etc, device, drug or drug combination and treatment schedule and dosage] wherein said treatment strategy includes at least one of types of treatment, device, drug combination, treatment schedule and dosage.

316. (Amended) A computer-implemented method of predicting progression of a biological process in an individual patient under a plurality of treatment protocols, wherein said biological process could be related to healthy or diseased processes, said plurality of protocols including no treatment, said method comprising:

creating a system model;

enumerating a plurality of treatment protocols; and

modifying the system model based on parameters specific to the individual.

selecting an optimal treatment protocol from said plurality of treatment protocols based on the modified system model ; and

predicting said progression based on the modified system model and selected optimal treatment protocol.

317. (Amended) The method of claim 316 wherein the step of creating a system model further comprises:

[realistically] modelling a biological process; and

[realistically] modelling the effects of the treatment on said biological process.

318. (Amended) The method of claim 317, wherein said step of modelling a biological process comprises creating a mathematical model for biological processes affecting healthy cell populations and creating a biological processes affecting diseased cell populations with at least one disease.

320. (Amended) The method of claim 318 wherein said diseased cell [populationss] populations with at least one disease is one of cancer cells, and diseased bone-marrow cells[including diseased Neutrophill cells and diseased Thrombocyte cells].

321. (Amended) The method of claim 317, wherein said treatment models comprise treatment specific processes that affect cell[populationss] populations.

322. (Amended) The method of claim 321 wherein said treatment specific process is interactions and associated biological processes involving one of a group [comprising] consisting of pharmacokinetic interactions and processes , pharmacodynamic interactions and processes, cytostatic interactions and processes, cytotoxic interactions and processes, and methods of affecting cell biology and causing cell death or cell replication[, with associated biological processes].

323. (Amended) The method of claim 316 wherein, said parameters specific to the individual include one or more selected from a group consisting of parameters related to [the] biological process dynamics, patient specific drug pharmacokinetics [PK], pharmacodynamics [PD], and dynamics of dose-limiting host tissues.

325. (Amended) A computer-implemented method of predicting progression of a biological process in a general patient under a plurality of treatment protocols, wherein said biological process could be related to healthy or diseased cells, said plurality of protocols

including no treatment, said method comprising:

creating a system model;

enumerating a plurality of treatment protocols; [and]

selecting an optimal treatment protocol from said plurality of treatment protocols based on the modified system model; and

predicting said progression based on the modified system model and selected optimal treatment protocol.

326. (Amended) The method of claim 325 wherein the step of creating a system model further comprises:

[realistically] modelling a biological process; and

[realistically] modelling the effects of the treatment on said biological process.

329. (Amended) The method of claim 327 wherein said cell populations with at least one disease is one of cancer cells, and bone-marrow cells [including at least one of diseased Neutrophill cells and diseased Thrombocyte cells].

331. (Amended) The method of claim 330 wherein said treatment specific process is interactions and associated biological processes involving one of a group [comprising] consisting of pharmacokinetic interactions and processes , pharmacodynamic interactions and processes , cytostatic interactions and processes, cytotoxic interactions and processes, and methods of affecting cell biology and causing cell death or cell replication [, with associated biological

241. (Amended) The system of claim 238 wherein the system comprises a model representing a tumor [is modelled as] the model comprising a combination of a plurality of [homogeneous group] groups of cells, each of said [homogeneous group] groups of cells representing a similarly behaving group of cells distributed between all the cell-cycle compartments.

242. (Amended) The system of claim 241, wherein the system is adapted to calculate in each step, a number of cells in each sub-compartment of each compartment of each group [is calculated] according to factors including a previous state, parameters of tumor, tumor current microenvironment and drug concentration.

244. (Amended) The system of claim 243, wherein the system is adapted to incorporate pharmacokinetic [PK] and pharmacodynamic [PD], cytostatic effects, cytotoxic effects, and other effects on cell disintegration of anticancer drugs [are incorporated into the model].

245. (Amended) The system of claim 244 wherein the system is adapted to incorporate a dose-limiting toxicity [is incorporated] into the model.

246. (Twice Amended) The system of claim 234 wherein, said parameters specific to the individual comprise parameters related to tumor dynamics, patient specific drug pharmacokinetic [PK], pharmacodynamic and dynamics of dose-limiting host tissues.

processes].

466. (Amended) A computer-implemented method for recommending an optimal treatment protocol for treating cancer using drugs, including chemotherapy, for an individual, said method comprising:

creating a cancer system model;

enumerating a plurality of treatment protocols for treating cancer using drugs [, including chemotherapy];

modifying the system model based on parameters specific to the individual; [and]

selecting an optimal treatment protocol from said plurality of treatment protocols based on the modified system model; and

recommending said optimal treatment.

467. (Amended) The method of claim 466 wherein the system model further comprises:

a [realistic] process model of cancer development; and

a [realistic] treatment model that models the effects of treating cancer with drugs, including chemotherapy.

472. (Amended) The method of claim 470 where a set control functions uniquely determine an outcome of every single step, wherein said control functions [depend on] comprise age of cells, state of a current population and associated environment.

473. (Amended) The method of claim 470 wherein a tumor is modelled as a combination of a plurality of [homogeneous group] groups of cells, each of said [homogeneous group] groups of cells representing a similarly behaving group of cells distributed between all the cell-cycle compartments.

476. (Amended) The method of claim 475, wherein pharmacokinetic [PK] and pharmacodynamic [PD],, cytotoxic effects,cytostatic effects and other effects on cell disintegration of anticancer drugs are incorporated into the model.

478. (Amended) The method of claim 466 wherein, said parameters specific to the individual comprise parameters related to tumor dynamics, patient specific drug pharmacokinetic [PK], pharmacodynamic, and dynamics of dose-limiting host tissues.

480. (Amended) A computer-implemented method of predicting a progression of cancer in an individual, said method comprising:

creating a cancer system model;

enumerating a plurality of treatment protocols for treating cancer using drugs, including chemotherapy;

modifying the system model based on parameters specific to the individual; [and]

selecting an optimal treatment protocol from said plurality of treatment protocols based on the modified system model; and

predicting said progression based on the modified system model and selected optimal

treatment protocol.

481. (Amended) The method of claim 480 wherein the system model further comprises:

a [realistic] process model of cancer development; and

a [realistic] treatment model that models the effects of treating cancer with drugs [, including chemotherapy].

486. (Amended) The method of claim 484 where a set control functions uniquely determine an outcome of every single step, wherein said control functions [depend on] comprise age of cells, state of a current population and associated environment.

487. (Amended) The method of claim 484 wherein a tumor is modelled as a combination of a plurality of [homogeneous group] groups of cells, each of said [homogeneous group] groups of cells representing a similarly behaving group of cells distributed between all the cell-cycle compartments.

490. (Amended) The method of claim 489, wherein pharmacokinetic [PK] and pharmacodynamic [PD], cytotoxic and other cell disintegration effects , and cytostatic effects of anticancer drugs are incorporated into the model.

492. (Amended) The method of claim 480 wherein, said parameters specific to the individual comprise parameters related to tumor dynamics, patient specific drug pharmacokinetic [PK], pharmacodynamic, and dynamics of dose-limiting host tissues.

494. (Amended) A computer-implemented method of predicting a progression of cancer in a general patient, said method comprising:

creating a cancer system model;

enumerating a plurality of treatment protocols for treating cancer using drugs[, including chemotherapy]; [and]

selecting an optimal treatment protocol from said plurality of treatment protocols based on the modified system model; and

predicting said progression based on the modified system model and selected optimal treatment protocol.

495. (Amended) The method of claim 494 wherein the system model further comprises:

a [realistic] process model of cancer development; and

a [realistic] treatment model that models the effects of treating cancer with drugs, including chemotherapy.

500. (Amended) The method of claim 498 where a set control functions uniquely determine an outcome of every single step, wherein said control functions [depend on] comprise

age of cells, state of a current population and associated environment.

501. (Amended) The method of claim 498 wherein a tumor is modelled as a combination of a plurality of [homogeneous group] groups of cells, each of said [homogeneous group] groups of cells representing a similarly behaving group of cells distributed between all the cell-cycle compartments.

504. (Amended) The method of claim 503, wherein pharmacokinetic [PK] and pharmacodynamic [PD], cytotoxic effects and cytostatic effects of anticancer drugs are incorporated into the model.

506. (Amended) A computer program product, including a computer readable medium, said program product comprising a set of instruction to enable a computer system to aid in recommending an optimal treatment protocol for an individual comprising:

a system model code;

treatment protocol generator code for generating a plurality of treatment protocols;

a system model modifier code , wherein said system model code is adapted to modify [is modified by] the system model [modifier] based on parameters specific to the individual to generate a modified system model code; and

a selector code to select an optimal treatment protocol from said plurality of treatment protocols based on the modified system model.

507. (Amended) The computer program product of claim 506 wherein the system model code further comprises:

a [realistic] biological process model code; and

a [realistic] treatment model code that enables a computer to model the effects of a treatment on the biological process.

508. (Amended) A computer program product, including a computer readable medium, said program product comprising a set of instructions to enable a computer system to aid in recommending an optimal treatment protocol for a general patient comprising:

a system model code;

treatment protocol generator code for a generating a plurality of treatment protocols; and

a selector code to select an optimal treatment protocol from said plurality of treatment protocols [based on the modified system model].

509. (Amended) The computer program product of claim 508 wherein the system model code further comprises:

a [realistic] biological process model code; and

a [realistic] treatment model code that enables a computer to model the effects of a treatment on the biological process.